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FAX COVER SHEET

DATE:	March 25, 2002	# OF PAGES:	1
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RE:	Serial No. 09/446,601 (Atty. Docket IVD 994)		

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♦MESSAGE♦

As discussed, attached are the following:

- **Response filed September 27, 2001**
- **Request for Extension of Time**
- **Return-receipt postcard**

#10 GR 3/29/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Abramovici et al.

Serial No.: 09/446,601

Filed: 03 April 2000

Group Art Unit: 1614

Examiner: D. Jagoe

CERTIFICATE UNDER 37 C.F.R. 1.8(a)
I hereby certify that this correspondence is being deposited on the date indicated below with the United States Postal Service as first class mail addressed to:

Assistant Commissioner for Patents,
Washington, DC 20231.

Paula H. Deckey
Name

September 27, 2001
Date

For: Solid Pharmaceutical Composition Containing Benzofuran Derivatives

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

RESPONSE

This is responsive to the Office Action mailed June 20, 2001 setting a three-month period for response.

Pursuant to the Petition for Extension of Time under 37 C.F.R. 1.136(a) submitted herewith, the period for response is extended one month to expire October 20, 2001. This response is therefore timely.

Claims 1-22 are in the application and are rejected under 35 U.S.C. 103(a) as being unpatentable over the Physician's Desk Reference (PDR) in view of Story et al., U.S. Patent No. 4,944,949 and Martin-Algarra et al., International Journal of Pharmaceutics 122, (1,2), 1 (1995) on the grounds that the PDR teaches an oral formulation of amiodarone tablets and that amiodarone is slightly soluble in water; that Story et al. teach a pharmaceutical delivery system of non-ionic hydrophilic surfactants for poorly water soluble active agents such as NSAIDs, and that Martin-Algarra et al. teach compositions of amiodarone in a non-ionic hydrophilic surfactant such as polysorbate 80. The Examiner maintains that it would have been obvious to have administered amiodarone orally in a non-ionic hydrophilic surfactant composition since the PDR teaches that amiodarone is slightly soluble in water and the surfactant systems of Story et al. demonstrate the solubilization of insoluble drugs such as NSAIDs, and because both the NSAIDs of Story et al. and the antiarrhythmics of the instant application are known to be poorly water soluble. Motivation to formulate amiodarone and

dronedarone in a hydrophilic anionic (sic. non-ionic) surfactant would come from the need for a rapidly absorbed orally available antiarrhythmic such as amiodarone. Additionally, absorption would be expected to be improved as taught by Martin-Algarra et al., thereby providing additional motivation.

The rejection is respectfully traversed and reconsideration thereof is requested. The PDR not only discloses that amiodarone is slightly soluble in water, as noted by the Examiner, but it also teaches that amiodarone is slowly and variably absorbed; that mean plasma concentrations include considerable individual variability, and that food significantly affects amiodarone absorption [e.g. it increases the area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) by a factor of 2.3 and 3.8, respectively and decreases the time to peak plasma concentration (T_{max}) by 37%]. This, of course, is the very problem addressed by applicants' invention. The absorption profile of amiodarone was known at least as early as 1985 when it was first approved for use, and yet, despite the 1990 Story et al. patent and the 1995 Martin-Algarra publication, the disclosures of which the Examiner urges would have made the solution provided by the instant invention obvious, the 2001 PDR entry for amiodarone indicates that the absorption problem has not yet been solved. In other words, although the slow and variable absorption by amiodarone has been known for more than 15 years and the teachings of Story et al. have been available for more than 10 years, increasing the absorption of amiodarone and reducing its variability have until now remained long-felt but unmet needs even with the additional motivation purportedly provided more than 5 years ago by Martin-Algarra et al. Had the cited prior art made the instant invention obvious, as urged by the Examiner, it would seem that the absorption problem related to amiodarone would have been solved long ago. Hence, it is respectfully submitted that the cited references would not have suggested applicants' invention.

More particularly, it is pointed out that the Story et al. disclosure is directed to the formulation of NSAIDs with surfactants to give micelle-forming compositions primarily intended to protect both the stomach and intestine. Such formulations are stated to contain drug and surfactant in a weight ratio (drug:surfactant) of from 1:5.7 to 1:50. Thus, relative to the active ingredient the surfactant is present in a wt% of from 570% to 5000% whereas the instant specification (p. 4, line 27, - p. 5, line 17) specifies that the surfactant is present in an amount of from 1% to 50%, preferably about 10%, by weight relative to the active principle. Clearly, there is nothing in Story et al. that would have suggested using such a small amount

of non-ionic hydrophilic surfactant to both increase rate and reduce variability of absorption of either NSAIDs or amiodarone and dronedarone.

The Martin-Algarra reference discloses use of the in situ rat gut technique to study the intestinal absorption of amiodarone. Neither an oral formulation nor oral administration are disclosed. The experiments were reportedly carried out using 0.4-80mM solutions of polysorbate 80 (ave. MW1310) containing 75 μg/ml of amiodarone hydrochloride which corresponds to solutions containing 0.5 – 105 mg/ml of polysorbate 80 and 0.075 mg/ml of amiodarone hydrochloride. Thus polysorbate 80 was present in a wt% of from 666% – 140,000% relative to the amiodarone hydrochloride. As pointed out hereinabove with regard to Story et al., surely nothing in Martin-Algarra would have suggested applicants' formulations containing from 1%-50% by weight relative to the active ingredient. Thus nothing in the cited references taken either singly or in combination would have suggested the invention here claimed.

Claims 1-22 are rejected for obviousness-type double patenting over claims 1-30 of U.S. Patent No. 6,143,778 on the grounds that the conflicting claims are not patentably distinct because both are drawn to a pharmaceutical composition of amiodarone and a non-ionic hydrophilic surfactant. The Examiner urges that although the amiodarone of the –778 patent is for parenteral administration, it would have been obvious to lyophilize the compositions of the patent and administer them orally. The rejection is traversed and reconsideration thereof is requested.

The claims of the –778 patent are drawn to parenteral solutions containing amiodarone hydrochloride, a buffer solution capable of maintaining a pH of 2.4-3.8 and a non-ionic hydrophilic surfactant. The role of the surfactant is to permit preparation of clear, stable, concentrated solutions of active principle which can be subsequently diluted for administration by perfusion. There is nothing in the reference to suggest lyophilizing the mixture of active agent, buffer and surfactant to prepare an oral preparation nor is there anything to suggest that oral administration of such a mixture would enhance the rate of absorption and reduce its variability. Thus there is nothing in the –778 patent that would render the instant claims obvious and hence the patent is not a proper basis for a double patenting rejection and the withdrawal thereof is respectfully requested.

There being no remaining issues, this application is believed in condition for favorable reconsideration an early allowance and such actions are earnestly solicited.

Respectfully submitted,

Dated: 9/27/01

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September 27, 2001

Response to Official Action (4pp); Petition for Extension of Time under 37 C.F.R. §1.136(a) (in duplicate); and Certificate under 37 C.F.R. §1.8

In re Patent Application of: Abramovici et al.

Serial No.: 09/446,601

Filed: 03 April 2000

PED/pld (Docket No. IVD 994)

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